REMARKS

Applicants are submitting this response to the Office Action dated January 26, 2005 and further in response to the Advisory Action issued on May 5, 2005. At the outset, the obvious-type double-patenting rejection has been overcome as indicated in the Advisory Action. However, the anticipation or, in the alternative, obviousness rejection remains pending.

More specifically, claims 1-3, 5-22, 24-43 and 45 remain rejected under 35 U.S.C. §102 or, in the alternative, under 35 U.S.C. § 103 as obvious over European Patent No. 0951915 A2 (European Patent). Applicants believe that this rejection should be withdrawn as discussed below in greater detail.

The dialysis solutions as claimed include separately formulated and sterilized solution parts that are combined to form a ready-to-use solution with enhanced biocompatibility. The solution parts include a first acidic solution part and a second acidic solution part wherein the first acidic solution part at least includes a dextrose concentrate and wherein the second acidic solution part at least includes a buffer concentrate, such as a lactate-based buffer. See, Specification, for example, page 9, lines 9-15.

Of the pending claims at issue, claims 1, 8, 17, 24, 30 and 40 are the sole independent claims. As previously provided, each of these claims has been amended and as amended now provides, in part, that the second acidic solution part including a buffer concentrate has a pH that is less than 5.5.

Applicants believe that the cited reference is distinguishable from the claimed invention. At a minimum, nowhere does this reference disclose or suggest a dialysis solution that is formulated from two acidic solution parts where a first solution part includes dextrose and the second solution part includes a buffer concentrate, such as a lactate-based concentrate, and wherein the second solution part has a pH that is less than 5.5. In contrast, the cited reference provides a buffer solution that has a pH of approximately between 6 and 8.5. See, European Patent, page 3, paragraph 19. Indeed, the reference effectively teaches away from a buffer solution with a pH that is less than 5.5 as claimed where the final resultant medical solution of the reference after mixing is substantially neutral, for example with a pH value between 6.5 and 7.5, preferably about 7.0. See, European Patent.

The Patent Office alleges that a pH of less than 5.5 associated with the second solution part as claimed is a minor variation of "approximately 6" as disclosed in the European Patent. See, Advisory Action. Applicants believe that the Patent Office characterization of the European Patent is improper and are submitting herewith an Affidavit of Leo Martis, Ph.D. in further support of this position. Therefore, Applicants believe that the cited art fails to anticipate and render obvious the claimed invention for at least these reasons.

Accordingly, Applicants respectfully request that the anticipation and alternative obviousness rejections in view of EP 0951915A2 be withdrawn.

For the foregoing reasons, Applicants respectfully submit that the present application is in condition for allowance and earnestly solicit reconsideration of same.

Respectfully submitted,

BELL, BOYD & LLOYD LLC

BY _____

Robert M. Barrett
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Dated: June 23, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Zieske et al.
Appl. No.:	10/628,065
Conf. No.:	4163
Filed:	July 25, 2003
Title:	DIALYSIS SOLUTIONS WITH REDUCED LEVELS OF GLUCOSE DEGRADATION PRODUCTS
Art Unit:	1623
Examiner:	E. Peselev
Docket No.:	DI-5924 (BBL No. 112713-429)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AFFIDAVIT OF LEO MARTIS, PH.D

I, Leo Martis, Ph.D., hereby state as follows:

1. I am a co-inventor of the above-referenced U.S. Patent Application No. 10/628,065 entitled "DIALYSIS SOLUTIONS WITH REDUCED LEVELS OF GLUCOSE DEGRADATION PRODUCTS." I earned a Ph.D. in pharmacology in 1973, a M.S. in pharmaceutical chemistry in 1970, and a B.S. in Chemistry in 1965. I have been a research chemist at Baxter International Inc. since 1974 and have been a research scientist working in the field of peritoneal dialysis solutions since 1978.

2. As one of the named inventors of the above-identified patent application, I am therefore familiar with the invention disclosed therein. I have recently reviewed the claims of the patent application as presently pending. A copy of the pending claims is attached hereto as Exhibit A.

3. The present invention generally relates to dialysis solutions that include separately formulated and sterilized solution parts that are combined to form a ready-to-use solution with enhanced biocompatibility. The dialysis solutions as claimed include a first acidic solution part and a second acidic solution part. The first acidic solution part at least includes a dextrose concentrate wherein the second acidic solution part includes a buffer concentrate, such as a lactate-based buffer. The second acidic solution part has a pH less than 5.5.

4. It is my understanding that the Patent Office has rejected pending claims 1-3, 5-22, 24-43 and 45 as allegedly anticipated or alternatively obvious. Attached hereto as Exhibit B is a copy of the Office Action dated January 26, 2005 and an Advisory Action dated May 5, 2005 that detail the rejection. More specifically, claims 1-3, 5-22, 24-43 and 45 have been rejected under 35 U.S.C. §102 as allegedly anticipated by or, in the alternative, under 35 U.S.C. §103 as allegedly obvious over European Patent No. 0951915A2 ("European Patent"). A copy of this reference is attached hereto as Exhibit C.

5. As one skilled in the art, I do not believe that the cited reference discloses or suggests the claimed invention. The basis for my opinion is set forth below.

6. In my opinion, a pH of less than 5.5 and associated with the second acidic solution part (e.g., buffer concentrate) as claimed is not a minor variation based on the European Patent. If the pH of approximately 6 for the buffer concentrate (e.g., first portion) in the European Patent were considered to cover a pH that is less than 5.5, this would require a pH of the second portion (e.g., glucose concentrate) of the medical solution in the European Patent to be greater than 6 in value. A pH of greater than 6 would be necessary to achieve a final neutral solution as further disclosed in the European Patent. See, European Patent, page 2, paragraph 7. Clearly, a pH of greater than 6 in the second portion is contrary to the European Patent where it specifies a pH-value of approximately between 3 and 6, preferably in the order of 3.5. See, European Patent, page 3, paragraph 19.

7. Further, I believe that the pH of the first portion (e.g., buffer concentrate) in the European Patent is required to be greater than 6. Again, this is necessary to provide a final resultant medical solution after mixing that is substantially neutral as further disclosed in the European Patent. See, Abstract. Even at the highest pH of 6 for the second solution part (e.g., glucose concentrate) as specified in the European Patent, this would require a pH that is greater than 6 for the first solution part (e.g., buffer concentrate) in order to provide a substantially neutral solution upon mixing. This is consistent with the example in the European Patent that includes a buffer solution part with a pH between 7 and 9 and a glucose concentrate with a pH between 3 and 6. See, European Patent, page 4, paragraphs 29 and 30.

8. At a buffer pH that is greater than 6 (e.g., 7 to 9), this contrasts the claimed invention that recites, in part, a buffer solution part with a pH that is less than 5.5. Even if the European Patent could be construed to cover a buffer pH of approximately 6 as the Patent Office argues, this would require the use of a glucose concentrate at a pH that is greater than 6 in order to provide a substantially neutral solution when mixed as provided in the European Patent and discussed above.

9. At a pH of greater than 6 for the glucose concentrate, this also contrasts the claimed invention that recites, in part, an acidic dextrose concentrate, such as an acidic dextrose concentrate having a pH that ranges from about 2.8 to about 3.8. The solution parts as claimed can than be sterilized to provide a mixed solution that has a reduced level of glucose degradation products. Therefore, in my opinion, the European Patent fails to disclose or suggest the dialysis solutions as required by the claimed invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: June 21, 2005

Leo Martis, Ph.D.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (currently amended): A dialysis solution comprising:

a first acidic solution including a dextrose concentrate; and

a second acidic solution including a buffer concentrate wherein the first acidic solution and the second acidic solution are admixed to form a ready-to-use dialysis solution~~.~~, and wherein the second acidic solution has a pH of less than 5.5.

Claim 2 (original): The dialysis solution of Claim 1 wherein the dextrose concentrate includes dextrose, calcium chloride, and magnesium chloride.

Claim 3 (original): The dialysis solution of Claim 1 wherein the buffer concentrate includes a lactate-based concentrate.

Claim 4 (canceled)

Claim 5 (original): The dialysis solution of Claim 1 wherein the ready-to-use dialysis solution includes about 1.5% to about 4.25% of dextrose.

Claim 6 (original): The dialysis solution of Claim 1 wherein the ready-to-use dialysis solution includes sodium and about 2.5 mEq/L to about 3.5 mEq/L of calcium.

Claim 7 (original): The dialysis solution of Claim 1 wherein the ready-to-use dialysis solution includes about 40 mEq/L of lactate.

Claim 8 (currently amended): A two part peritoneal dialysis solution comprising:

a first part including an acidic concentrate that includes dextrose; and

a second part including a lactate-based buffer concentrate having a pH of less than ~~7.0~~5.5 wherein the first part and the second part are admixed prior to infusion into a patient.

Claim 9 (original): The two part peritoneal dialysis solution of Claim 8 wherein the pH of the first part ranges from about 2.8 to about 3.8.

Claim 10 (original): The two part peritoneal dialysis solution of Claim 9 wherein the pH of the first part ranges from about 3.0 to about 3.5.

Claim 11 (original): The two part peritoneal dialysis solution of Claim 8 wherein the acidic concentrate further includes calcium chloride and magnesium chloride.

Claim 12 (currently amended): The two part peritoneal dialysis solution of Claim 8 wherein the lactate-based buffer concentrate has a pH that ranges from about 5.0 to ~~about~~less than 5.5.

Claim 13 (original): The two part peritoneal dialysis solution of Claim 8 wherein the acidic concentrate includes about 30.0 g/L to about 85.0 g/L of dextrose, calcium chloride dihydrate, and magnesium chloride hexahydrate.

Claim 14 (original): The two part peritoneal dialysis solution of Claim 13 wherein the acidic concentrate includes about 7.0 mEq/L of calcium.

Claim 15 (original): The two part peritoneal dialysis solution of Claim 13 wherein the acidic concentrate includes about 5.0 mEq/L of calcium.

Claim 16 (original): The two part peritoneal dialysis solution of Claim 8 wherein the lactate-based buffer concentrate includes sodium chloride and sodium lactate.

Claim 17 (currently amended): A two part peritoneal dialysis solution comprising:

a first part housed in a first structure, the first part including an acidic dextrose concentrate; and

a second part housed in a second structure, the second part including an acidic buffer concentrate wherein the first part and the second part are separately sterilized and admixed to form a ready-to-use peritoneal dialysis solution~~.~~ ,and wherein the second part has a pH that is less than 5.5.

Claim 18 (original): The two part peritoneal dialysis solution of Claim 17 wherein the first part and the second part are stored in a multi-chamber container including the first structure and the second structure adaptedly coupled such that the first part and the second part are capable of mixing to form the mixed solution prior to infusion into the patient.

Claim 19 (original): The two part peritoneal dialysis solution of Claim 17 wherein the first structure and the second structure each include a solution bag capable of being coupled to an admix device allowing mixing of the first part and the second part to form the mixed solution.

Claim 20 (original): The two part peritoneal dialysis solution of Claim 17 wherein the ready-to-use peritoneal dialysis solution includes about 1.5% to about 4.25% of dextrose.

Claim 21 (original): The two part peritoneal dialysis solution of Claim 20 wherein the ready-to-use peritoneal dialysis solution further includes sodium, calcium, chloride, magnesium and lactate.

Claim 22 (original): The two part peritoneal dialysis solution of Claim 17 wherein the acidic dextrose concentrate includes dextrose, calcium chloride and magnesium chloride at a pH ranging from about 2.8 to about 3.8.

Claim 23 (canceled)

Claim 24 (currently amended): A method of producing a dialysis solution, the method comprising the steps of:

formulating an acidic concentrate and a buffer concentrate having a pH of less than ~~7.0~~5.5 wherein the acidic concentrate at least includes dextrose;

separately sterilizing the acidic concentrate and the buffer concentrate; and

mixing the acidic concentrate and the buffer concentrate.

Claim 25 (original): The method of Claim 24 wherein the acidic concentrate and the buffer concentrate are each housed in a respective chamber of a multi-chambered container adaptedly coupled such that the acidic concentrate and the lactate-based buffer concentrate can be mixed within the multi-chambered container.

Claim 26 (original): The method of Claim 24 wherein the acidic concentrate and the buffer concentrate are each housed in a respective solution bag each capable of being coupled to an admix device allowing mixing of the acidic concentrate and the lactate-based buffer concentrate.

Claim 27 (original): The method of Claim 24 wherein the acidic concentrate has a pH ranging from about 2.8 to about 3.8.

Claim 28 (original): The method of Claim 24 wherein the acidic concentrate further includes calcium chloride and magnesium chloride.

Claim 29 (currently amended): The method of Claim 24 wherein the buffer concentrate includes a lactate-based concentrate at a pH that ranges from about 5.0 to ~~about~~less than 5.5.

Claim 30 (currently amended): A method of modifying a standard dialysis solution comprising the steps of:

formulating two or more solution parts of the standard dialysis solution wherein the solution parts at least include a dextrose concentrate and a buffer concentrate;

separately sterilizing the dextrose concentrate and the buffer concentrate at a pH of less than ~~7.0~~5.5; and

mixing the dextrose concentrate and the buffer concentrate to produce a modified standard dialysis solution.

Claim 31 (original): The method of Claim 30 wherein the modified standard dialysis solution includes fewer glucose degradation products than the standard dialysis solution.

Claim 32 (original): The method of Claim 31 wherein the glucose degradation products are selected from the group consisting of 5-hydroxymethyl furfural, 3-deoxyglucasone, glyoxal, methylglyoxal, acetaldehyde and combinations thereof.

Claim 33 (original): The method of Claim 30 wherein the modified standard dialysis solution includes a solution composition that is substantially the same as the standard dialysis solution except for the glucose degradation products.

Claim 34 (original): The method of Claim 30 wherein the modified standard dialysis solution includes about 1.5% to about 4.25% of dextrose.

Claim 35 (original): The method of Claim 30 wherein the modified standard dialysis solution further includes sodium, calcium, magnesium, chloride, and lactate.

Claim 36 (original): The method of Claim 30 wherein the dextrose concentrate is sterilized at a pH that ranges from about 2.8 to about 3.8.

Claim 37 (original): The method of Claim 30 wherein the buffer concentrate includes a lactate-based concentrate.

Claim 38 (original): The method of Claim 37 wherein the lactate-based concentrate includes sodium lactate and sodium chloride.

Claim 39 (original): The method of Claim 30 wherein the dextrose concentrate includes dextrose, calcium chloride and magnesium chloride.

Claim 40 (currently amended): A method of providing dialysis to a patient comprising the steps of:

mixing an acidic dextrose concentrate and an acidic buffer solution to form a ready-to-use dialysis solution wherein the acidic dextrose concentrate and the acidic buffer concentrate are separately sterilized prior to mixing and wherein the acidic buffer concentrate has a pH that is less than 5.5; and

using the ready-to-use dialysis solution during dialysis.

Claim 41 (original): The method of Claim 40 wherein the ready-to-use dialysis solution is used as a dialysate.

Claim 42 (original): The method of Claim 40 wherein the ready-to-use dialysis solution is infused into the patient during peritoneal dialysis.

Claim 43 (original): The method of Claim 40 wherein the acidic dextrose concentrate includes dextrose, calcium chloride, and magnesium chloride.

Claim 44 (canceled)

Claim 45 (original): The method of Claim 40 wherein the acidic solution has a pH ranging from about 2.8 to about 3.8.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,065	07/25/2003	Paul Zieske	DI-5924	4163

29200 7590 05/05/2005

BAXTER HEALTHCARE CORPORATION
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EXAMINER	
PESELEV, ELLI	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 05/05/2005

DOCKETED

Please find below and/or attached an Office communication concerning this application or proceeding.

Pak 5/12/05

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/628,065	Applicant(s) ZIESKE ET AL.	
	Examiner Elli Peselev	Art Unit 1623	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

THE REPLY FILED 25 April 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-3,5-22,24-43 and 45*.

   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: a pH of less than 6.5 encompassed by the instant claims is a minor variation of "approximately 6" disclosed by the European Patent. Applicant has not presented any evidence to show that such a minor variation in pH would produce in a composition having a patentably distinct difference. The obvious-type double patenting rejection is deemed to be overcome by the present amendment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

ELLI PESELEV
PRIMARY EXAMINER
GROUP 1200

UNITED STATES PATENT AND TRADEMARK OFFICE

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10/628,065	07/25/2003	Paul Zeske	DI-5924	4163

29176 7590 01/26/2005

BELL, BOYD & LLOYD LLC
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EXAMINER	
PESELEV, ELLI	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 01/26/2005

DUE: 4-26-05

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/628,065	ZIESKE ET AL.	
	Examiner	Art Unit	
	Elli Peselev	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-45 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 10/327,264 for the reasons set forth in the Office Action of August 31, 2004.

Applicant's arguments filed December 2, 2004 have been considered but have not been found persuasive.

Applicant contends that the subject matter as defined by claims 1-42 of the copending application recites solutions with a pH ranging from 7.0 to about 12.0. This argument has not been found persuasive since claim 1, for example, recites the pH as being "about 7". About 7.0 encompasses 6.5, which is acidified pH.

Claims 1-45 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the European Patent No. 0 951 915 A2 for the reasons set forth in the Office Action of August 31, 2004.

Applicant's arguments filed December 2, 2004 have been considered but have not been found persuasive.

Page 3 of the European patent discloses a solution containing a first solution containing dextrose having pH of approximately 3-6 and a second solution containing buffer having pH of approximately 6-8.5 pH. The pH of approximately 6 is an acidified pH. Note also that a pH of "about 5.5" as recited in claim 4 is not distinct from "approximately 6" as disclosed by the European Patent. Further note that, for example, claim 8 recites the pH of the second solution being "less than 7" which is within the scope of the pH of 6 disclosed by the European Patent and claims 1, 17 and 40 do not

recite a specific pH. Therefore, the claimed solutions and methods are still anticipated by or are deemed prima facie obvious over the European Patent.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elli Peselev whose telephone number is (571) 272-0659. The examiner can normally be reached on 9.00-5.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elli Peselev

ELLI PESELEV
PRIMARY EXAMINER
GROUP 1200

INFORMATION DISCLOSURE CITATION IN AN APPLICATION (Use several sheets if necessary) PTO Form 1449	Atty Docket No. DI-5927	Application No. 10/628,065
	Applicant Zieske et al.	
	Filing Date July 25, 2003	Group 1614

U.S. PATENT DOCUMENTS

Examiner's Initials		Document Number	Publication Date	Inventor	Class	Subclass	Filing Date If Appropriate
GP		6,309,673	10-30-01	Duponchelle et al.			
GP		6,277,815	08-21-01	Knerr			

FOREIGN PATENT DOCUMENTS

Examiner's Initials		Document Number	Publication Date	Country	Class	Subclass	Translation Yes	Translation No
GP		EP 1 008 341 A1	06-14-00	Europe				
GP		WO 00/23086	04-27-00	PCT				
GP		JP 2000-245826	09-12-00	Japan				

Examiner's Initials		**OTHER DOCUMENTS** *(Including Author, Title, Date, Pertinent Pages, Etc.)*
GP		Zheng et al., Heat sterilization of peritoneal dialysis solutions influences ingestive behavior in non-uremic rats, Kidney International, Vol. 62 (2002), pp. 1447-1453.

Examiner: G. Parker	Date Considered: 1/13/2005

*Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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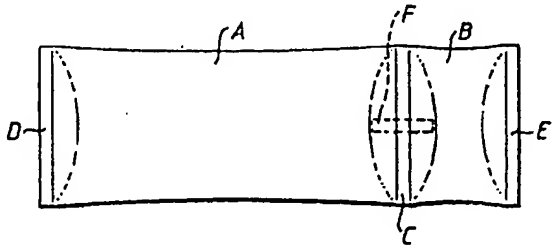
(54) System and method for providing a sterile medical solution containing glucose orglucose-like compounds

(57) System for providing a sterile medical solution, for example nutritional solution or a solution for peritoneal dialysis, containing glucose or glucose-like compounds and further substances, comprising a first package (A) containing a first portion of the medical solution and a second package (B) containing a second portion of the medical solution. The second portion comprising said glucose or glucose-like compounds, thereafter the first and second packages are heat-sterilised and the first and second portions are mixed to form that sterile medical solution. The first and second portions of the medical solution in the first and second packages (A,B) have such respective pH-values that the final resultant medical solution after mixing is substantially neutral, for example with a pH-value between 6,5 and 7,5, preferably about 7,0.

Fig.1



EP 0 951 915 A2

Description

TECHNICAL FIELD

[0001] The present invention relates to a system for providing a sterile medical solution comprising glucose or glucose-like compounds, for example nutritional solutions or solutions for peritoneal dialysis. A first portion of the solution is packed in a first package whilst a second portion of the solution comprising the glucose or the glucose-like compounds is packed separately in a second package, whereafter the two packages are heat sterilized and the first and second portions are mixed to form the sterile medical solution. By the expression glucose-like compounds is meant for example glucose polymers.

BACKGROUND OF THE INVENTION

[0002] It is known to pack a CAPD-solution in a two chamber package from, for example, the article "In Vitro Testing of a Potentially Biocompatible Continuous Ambulatory Peritoneal kDialysis Fluid" by N Topey et al, in Nephrol Dial Transplant (1991) 6:574-581.

[0003] The same, or at least a similar, two chamber package having essentially the same inventors is described in international patent application no. WO 91/08008. From e.g. Example 1 of this document it is apparent that the two parts of the package are intended to contain essentially the same quantity of solution. Thus, when the article refers to a larger and smaller package respectively, this is assumed to mean that even in this case the two packages will contain the same quantity of solution, though with the one package being made larger so as to be able to serve as a mixing chamber.

[0004] It is known from, for example, the article "Toxity of peritoneal dialysis fluids on cultured fibroblasts L-929" by Anders Wieslander et al, in Kidney International, Vol 40 (1991) pp 77-79, that heat sterilized CAPD-solutions can contain harmful components which can depend on the decomposition of certain compounds, for example glucose, during the sterilization.

[0005] It is known from, for example, US Patent 4 369 779 and 4 753 697 to achieve a sterile coupling between two tubes in various ways, which can be joined to two separate packages.

DISCLOSURE OF THE INVENTION

[0006] The present invention can be said to be a development of the above mentioned teachings and relates to a system for providing a sterile medical solution, for example a nutritional solution or a solution for peritoneal dialysis, containing glucose or glucose-like compounds and further substances, comprising a first package (A) containing a first portion of the medical solution and a second package (B) containing a second portion of the medical solution, said second portion comprising said glucose or glucose-like compounds, whereafter the first and second packages are heat sterilised and the first and second portions are mixed to form said sterile medical solution. The invention is characterised in that the first and second portions of the medical solution in the first and second packages (A,B) have such respective pH-values that the final resultant medical solution after mixing is substantially neutral, for example with a pH-value between 6,5 and 7,5, preferably about 7,0.

[0007] In this manner it is possible to achieve a final neutral solution with a pH between 6,5 and 7,5. Preferably, a pH of 7,0 is hereby achieved. Here it should be stressed that as far as we are aware no such neutral solutions for PD-dialysis are presently commercially available on the market.

[0008] Suitably, the contents of the second, smaller glucose-containing package have a pH-value of approximately between 3 and 6, preferably in the order of 3,5, and are maintained at that low pH during sterilisation. At the same time, the contents of the first, larger package has a pH-value of approximately between 6 and 8,5.

[0009] After sterilization, mixing and diluting to 1,5% glucose content, the medical solution has an absorbency caused by breakdown products from glucose at 228 nm of less than 0,35 and preferably 0,20 or lower.

[0010] Alternatively the medical solution, after sterilization, mixing and diluting to 1,5% glucose content, has an ICG-value (Inhibition of Cell Growth tested on cultured fibroblasts L-929) caused by breakdown products from glucose of less than 50%, preferably less than 30%. The reason for this definition is that the degree of inhibited cell growth bears a close relation to the UV-absorbency at 228 nm. It must however be taken into consideration that the solution should not contain compounds other than glucose or glucose-like compounds with absorbency at 228 nm. Should the solution contain other such compounds, then the absorbency will be affected. With knowledge of the included compounds it can however be calculated how much of the absorbency is dependent on breakdown products from glucose.

[0011] Alternatively, the medical solution, after sterilisation, mixing and diluting to a glucose content of 1,5% by weight, contains a quantity of acetaldehyde with a ppm-value less than 1,0, suitably less than 0,1 and preferably in the order of 0,01-0,001.

[0012] Advantageously, the glucose or glucose-like compounds in the second portion of the medical solution in the second package (B) have a concentration of greater than 20% by weight so that the formation of toxic substances during said sterilisation is substantially prevented therein.

[0013] Preferably, the content of the glucose or glucose-like compounds in the second package (B) has a concentration in the order of 40% by weight.

[0014] In practice, it has been shown to be possible to make use of a sterilizing temperature between 110°C and 150°C and sterilizing times between 180 minutes and 10 minutes from the commencement of heating to cooling to room temperature. The time interval for the maximum heating should hereby be kept as short as possible, though sufficiently long, of course, to meet the requirements imposed by the authorities so that sufficient death rate of bacteria and spores is obtained.

[0015] One possibility is that the two packages are manufactured separately and each one provided with a connection piece or connection tube. Preferably, both packages are completely sealed and each one provided with a connection piece or connection tube made from a heat sealable material and sealed at its extremity with a welded seal, which is intended to be removed or opened under maintained sterility for connection of the two packages together and mixing of their contents. Equipment and procedure for such a connection are described in the above mentioned US patents. The invention does however also include other known sterile connections, for example such as those which are nowadays used for CAPD. An advantage with this embodiment is that the smaller package can be separately heat sterilized at a high temperature for a short period with a short heating period and a short cooling period.

[0016] Alternatively, the second package containing said glucose or glucose-like compounds can form a minor part of a double package, for example a double bag, the other part of which forms the first package. The two parts can then be made to communicate with each other for mixing of the contents. The first package should thereby have such volume that in addition to its original contents, it can also accommodate the contents of the second package. An advantage with this embodiment is that an openable connection conduit can be arranged between the two packages already during their manufacture. The heating up time for the smaller package will however be somewhat dependent on the heating up time of the larger package. Even in this case, however, it is desirable that the sterilisation temperature is kept high and the heating up time short.

[0017] Where the solution according to the invention is intended for peritoneal dialysis the system according to the invention can comprise a smaller package containing 20-500 ml, preferably approximately 65-75 ml glucose concentrate with a pH of approximately 3-6, preferably approximately 3,5 and a glucose content of 10-70%, preferably approximately 40%, as well as a larger package containing the remaining compounds, for example Na-lactate 9g, NaCl 10,8g, $CaCl_2$ 380 mg and $MgCl_2$ 102 mg, with a pH adjusted to a desired value between 6 and 8,5, and preferably distilled water in a quantity in the order of 2 litres, for example 1935-1925 ml.

[0018] The invention also relates to a method for providing a sterile medical solution, for example a nutritional solution or a solution for peritoneal dialysis, containing glucose or glucose-like compounds and further substances, comprising providing a first portion of the medical solution in a first package (A) and a second portion of the medical solution in a second package (B) comprising said glucose or glucose-like compounds; heat sterilising said first and second packages; and interconnecting said first and second packages for combining said first and second portions for forming said sterile medical solution. According to the invention, the first and second portions of the medical solution in the first and second packages (A,B) have such respective pH-values that the final resultant medical solution after mixing is substantially neutral, for example with a pH-value between 6,5 and 7,5, preferably about 7,0.

[0019] Suitably, the second portion of the medical solution in the second package (B) has a pH-value of approximately between 3 and 6, preferably in the order of 3,5, and the first portion of the medical solution in the first package (A) has a pH-value of approximately between 6 and 8,5.

[0020] In a prefered embodiment, the second package (B) is sterilised at a temperature between 110°C and 150°C, preferably above 120°C.

Advantageously, the second package (B) is sterilised during a time interval of 180 to 10 minutes from initiation of heating to cooling to room temperature.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021]

Fig. 1 shows a double package intended to be used in connection with the system according to the invention.

Fig. 2 shows an alternative in the form of two separate bags.

Fig. 3 illustrates the relationship between the glucose content and the ICG-value after heat sterilising of glucose dissolved in pure water.

Fig. 4 shows the relationship between the ICG-value and the UV-absorbency at 228 nm after heat sterilizing solutions having different glucose content in pure water.

Fig. 5 shows the absorbency at 228 nm after heat sterilizing solutions with different glucose contents in pure water.

Fig. 6 shows in the form of a bar chart a comparison between the ICG-values after heat sterilizing water solutions with 1,5% and 40% glucose respectively.

Fig. 7 illustrates in the same manner a comparison between the absorbency at 228 nm after heat sterilizing water solutions with 1,5% and 40% glucose respectively.

BEST MODE OF CARRYING OUT THE INVENTION

[0022] From the above mentioned article by Anders Wieslander et al. it is apparent that existing commercial glucose solutions inhibit the growth of cultured fibroblasts. This implies that the glucose solutions contain one ore more substances that are toxic in the biological system.

[0023] From a comparison of, for example, sterile filtered solutions and heat sterilized solutions with essentially the same contents, it appears that the toxic effect depends on the substances formed in connection with the heat sterilization or the subsequent storage. Here it should be noted that the authorities in many countries require a sterilization after packaging of the product. In principle this is not possible with sterile filtered solutions.

[0024] From, for example, the graph in Fig. 4 it can be seen that the toxic effect (percentage inhibited growth), and thereby also the quantity of toxic substances, is related to the absorbency at 228 nm. This implies that a glucose solution with low absorbency is, from a toxicological view, probably better than a solution with high absorbency at 228 nm.

[0025] The aim has been to provide a glucose solution with a considerably lower toxic effect on the biological system compared with sterile glucose solutions commercially available until now. By low toxicity is meant that, according to the invention, a glucose solution diluted to a glucose content of 1,5% may not inhibit cell growth of cultures fibroblasts L-929 through breakdown products (tested according to the above mentioned article by Anders Wieslander et al.) by more than 50% and preferably by no more than 30%.

[0026] Two alternative bag systems are shown in Figs. 1 and 2 which can form the above mentioned packages. In Fig. 1 a double bag is shown consisting of a larger part A and a smaller part B that are separated by a weld or other seal C. The ends of the double package are sealed in a similar manner by welds or other means D,E respectively. The weld C can be entirely break-openable. Alternatively, the two bag parts A and B can be connected already during manufacture by means of a tube F containing a suitable breakable seal, for example a conventional breakpin.

[0027] The alternative shown in Fig. 2 consists of a separate larger bag A and a similarly separate smaller bag B. The two bags are provided with connection pieces or connection conduits denoted by G and H respectively. Each of these connection pieces can be provided with sterile connecting valves for sterile connection. In the shown example it is intended that they be terminated with an end sealing weld I,J respectively. A sterile connection can thus be achieved in the manner described by way of example in said above mentioned American patents.

[0028] The alternative according to Fig. 2 enjoys the advantage that the bag A can be heat sterilized in a conventional manner at the same time that a particularly quick heating and cooling of the bag B can be achieved if it is manufactured from two plastic sheets laid one on top of the other which are joined to each other along the periphery and which have dimensions such that the layer of glucose solution can be maintained relatively thin during the heat sterilization. By way of example, a bag containing 75 ml of glucose solution can have the dimensions 10 cm by 10 cm.

[0029] The larger bag A can, if used in peritoneal dialysis, contain a salt solution with the contents Na-lactate 9g, NaCl 10,8g, $CaCl_2$ 380 mg and $MgCl_2$ 102 mg (the composition can be varied somewhat). The pH should be adjusted to the desired value between 7 and 9. Finally, the bag preferably contains distilled water in a quantity in the order of 2 litres, for example 1925-1935 ml. The heat sterilization is envisaged to take place in a conventional manner in an autoclave with suitable adapted time and temperatures.

[0030] The small bag B can contain glucose concentrate, for example 20-500 ml, preferably 65-75 ml, 10-70% glucose, preferably 40%. The pH-value should lie between 3 and 6, preferably about 3,5. The sterilization may be effected in an autoclave at a temperature between 100°C and 145°C, suitably above 120°C and preferably at 130°C. With the embodiment according to Fig. 1 the bag part B is of course sterilized at the same time as the bag part A. With the embodiment according to Fig. 2, the bag B is however suitably sterilized separately so that the necessary sterilizing temperature can be quickly reached and thereafter obtain a quick cooling.

[0031] During the trials F_0 equal to 40 was sought, though in practice this value varied somewhat. By F_0 is meant the time in minutes which the solution should need to be maintained at 121°C in order to become sterile in accordance with that which is demanded by supervising authorities. F_0 equal to 10 implies therefore that the product must be maintained at 121°C for 10 minutes in order to achieve sterility.

[0032] The following table presents the results of a number of experimental tests. In line 1 a sterile-filtered, i.e. non-heat sterilized, complete solution for PD containing 1,5% glucose was tested. The three following lines show the results with heat sterilization with differing F_0 of a complete PD-solution in which the glucose was added at the beginning. These solutions also included 1,5% glucose.

[0033] The last three lines give the results of tests on complete mixing with which a glucose solution was heat steri-

lized separately so that first after sterilizing it could be mixed with remaining compounds included in the PD-solution. The glucose concentration was hereby maintained during the sterilizing at about 40%. After the mixing together, this was reduced to 1,5% in agreement with the concentration of remaining solutions in the comparative tests.

[0034] From the table it can further be seen that with help of the invention the concentration of acetaldehyde can be kept low by separately sterilising the glucose solution. Acetaldehyde is a typical breakdown product from glucose and the amount of this product should be kept below 1,0 ppm, suitably below 0,1 ppm and preferably in the order of 0,01-0,001 ppm.

[0035] In Fig. 4 the relationship is shown between the absorbency at 228 nm and the ICG-values after heat sterilising of a number of glucose solutions in pure water. The graph shows that the conditions for an acceptable product can either be defined by means of a low absorbency value or low ICG-value.

[0036] Fig. 5 shows the absorbency at 228 nm after heat-sterilising for a number of glucose solutions in pure water. The higher the glucose concentration is maintained, the lower the adsorbency and thus also the ICG-value becomes. In practice, however, the glucose concentration should not be maintained above about 40%. In addition, particularly at low temperatures there is a risk of crystal-formation.

[0037] Finally, Figs. 6 and 7 show respectively a comparison between the absorbency values at 228 nm for a sterilized water solution with 1,5% glucose in complete condition and a corresponding 1,5% solution in which the glucose was sterilized separately at a concentration of 40%.

[0038] The invention has been described in the above particularly in connection with peritoneal dialysis, more particularly CAPD. It will however be apparent that the invention can also be suitable in connection with other sterile solutions containing glucose or glucose-like compounds, for example polymers of glucose. By way of example the invention can be suitable in connection with sterilization of nutritional solutions containing glucose or glucose-like compounds which otherwise will be problematic in terms of breakdown products in connection with heat sterilization.

Table

The toxicity and breakdown products in PD-solutions after heat sterilizing. The PD-solutions were sterilized either as a conventional bag or double bag with glucose concentrate. All values refer to finally mixed end products.

Test solution	F_0	Absorbency Acetaldehyde ppm			Formaldehyde ppm	Cytotoxicity %
		228 nm	284 nm			
sterile-filtered	0	0.295	0.011	0.005	<0.005	16
Complete	10	0.467	0.053	4.0	0.005	44
Complete	20	0.666	0.110	8.8	0.005	73
Complete	30	0.765	0.150	11.6	0.2	83
Glucose conc	10	0.404	0.074	0.005	<0.005	21
Glucose conc	20	0.419	0.112	0.005	<0.005	25
Glucose conc	30	0.414	0.158	0.005	<0.005	27

Claims

1. System for providing a sterile medical solution, for example a nutritional solution or a solution for peritoneal dialysis, containing glucose or glucose-like compounds and further substances, comprising a first package (A) containing a first portion of the medical solution and a second package (B) containing a second portion of the medical solution, said second portion comprising said glucose or glucose-like compounds, whereafter the first and second packages are heat sterilised and the first and second portions are mixed to form said sterile medical solution, **characterised in that** the first and second portions of the medical solution in the first and second packages (A,B) have such respective pH-values that the final resultant medical solution after mixing is substantially neutral, for example with a pH-value between 6,5 and 7,5, preferably about 7,0.

2. System according to claim 1, **characterised in that** the second portion of the medical solution in the second package (B) has a pH-value of approximately between 3 and 6, preferably in the order of 3,5, and that the first portion of the medical solution in the first package (A) has a pH-value of approximately between 6 and 8,5.

3. System according to anyone of the preceeding claims, **characterised** in that the medical solution after sterilisation,

mixing and diluting to a glucose content of 1,5% by weight, has an absorbency caused by breakdown products from glucose at 228 nm of less than 0,35 and preferably in the order of 0,20 or lower.

4. System according to anyone of claims 1-2, **characterised** in that the medical solution, after sterilisation, mixing and dilution to a glucose content of 1,5% by weight, has an ICG-value (Inhibition of Cell Growth tested on cultured fibroblasts L-929) caused by breakdown products from glucose of less than 50%, preferably of less than 30%.

5. System according to anyone of claims 1-2, **characterised** in that the medical solution, after sterilisation, mixing and diluting to a glucose content of 1,5% by weight, contains a quantity of acetaldehyde with a ppm-value less than 1,0, suitably less than 0,1 and preferably in the order of 0,01-0,001.

6. System according to any one of the preceding claims, **characterised in that** the glucose or glucose-like compounds in the second portion of the medical solution in the second package (B) has a concentration of greater than 20% by weight so that the formation of toxic substances during said sterilisation is substantially prevented therein.

7. System according to claim 6, **characterised in that** the content of the glucose or glucose-like compounds in the second package (B) has a concentration in the order of 40% by weight.

8. System according to anyone of the preceding claims, **characterised in that** said first package (A) has a volume sufficient to accommodate both said first and said second portions of said medical solution.

9. System according to anyone of the preceding claims, **characterised in that** said second package (B) contains 20 to 500 ml, preferably approximately 65-75 ml glucose concentrate, and said first package (A) contains said further substances, for example Na-lactate 9g, NaCl 10,8g, $CaCl_2$ 380 mg and $MgCl_2$ 102 mg, and about 2 litres of water.

10. System according to anyone of the preceding claims, **characterised in that** the first and second packages (A, B) are disposed with respect to each other in a manner such that the second package (B) can be separately heat sterilised from the first package (A) at a higher temperature and in a shorter time than the first package (A).

11. System according to any one of the preceding claims, **characterised in that** the first and second packages are completely sealed and are provided with each a connection piece or connection tube (G, H respectively) made from a heat sealable material and closed at its extremity with a sealing weld (I, J respectively), which is intended to be removed or opened during maintained sterility for interconnection of the two packages (A and B) and mixing of their contents.

12. System according to any one of claims 1 - 10, **characterised in that** said first and second packages (A, B) comprises separate portions of a single package comprising a double bag, and in that said second package (B) containing said glucose or glucose-like compounds is smaller than the first package (A).

13. System according to claim 12, **characterised in that** said first and second packackages (A, B) comprises a connection means for interconnection of the two packages after sterlisation.

14. System according to claim 13, **characterised in that** said connection means is a breakable seal, for example a breakpin.

15. Method for providing a sterile medical solution, for example a nutritional solution or a solution for peritoneal dialysis, containing glucose or glucose-like compounds and further substances, comprising:

providing a first portion of the medical solution in a first package (A) and a second portion of the medical solution in a second package (B) comprising said glucose or glucose-like compounds,
heat sterilising said first and second packages; and
interconnecting said first and second packages for combining said first and second portions for forming said sterile medical solution,
characterised in that the first and second portions of the medical solution in the first and second packages (A,B) have such respective pH-values that the final resultant medical solution after mixing is substantially neutral, for example with a pH-value between 6,5 and 7,5, preferably about 7,0.

16. Method according to claim 15, **characterised in that** the second portion of the medical solution in the second

package (B) has a pH-value of approximately between 3 and 6, preferably in the order of 3,5, and that the first portion of the medical solution in the first package (A) has a pH-value of approximately between 6 and 8,5.

17. Method according to anyone of claims 15 - 16, **characterised in that** said second package (B) is sterilised at a temperature between 110°C and 150°C, preferably above 120°C.

18. Method according to anyone of claims 15 - 17, **characterised in that** said second package (B) is sterilised during a time interval of 180 to 10 minutes from initiation of heating to cooling to room temperature.

Fig.1

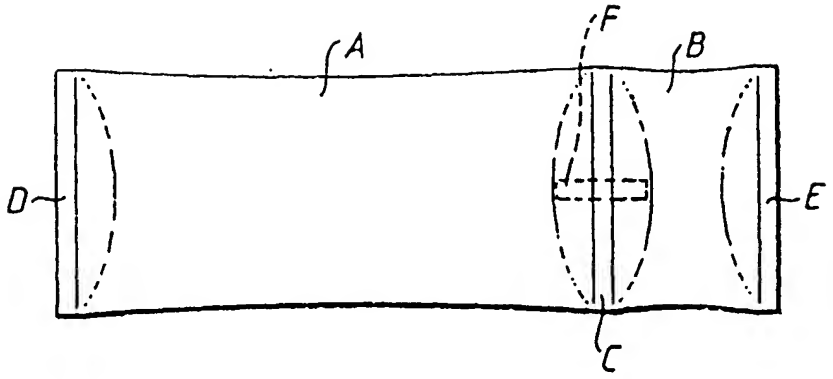


Fig.2

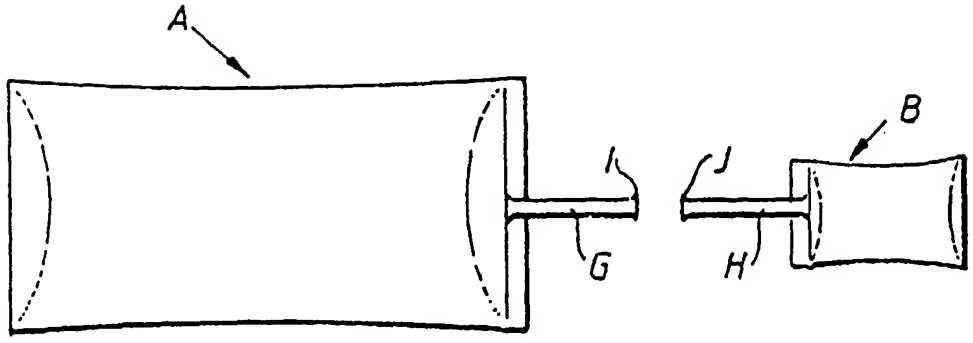


Fig.3

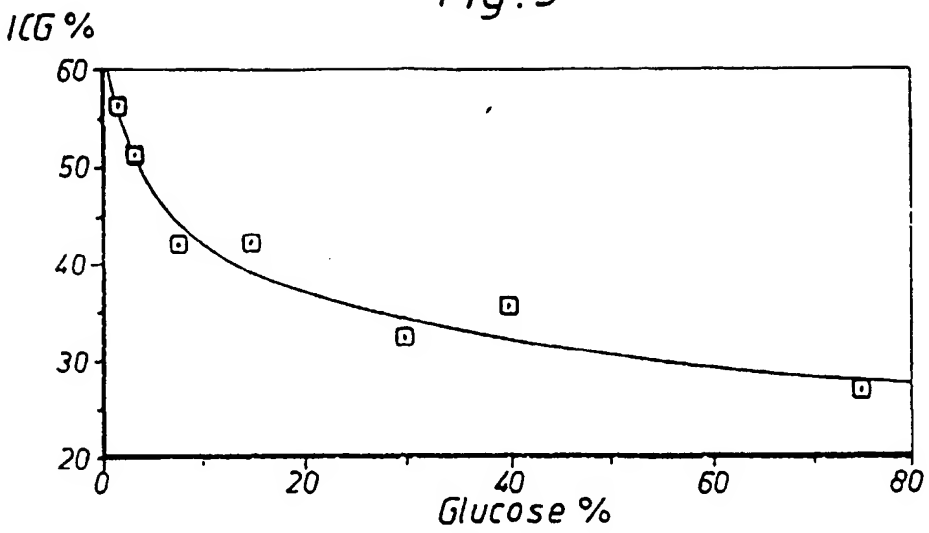


Fig.4

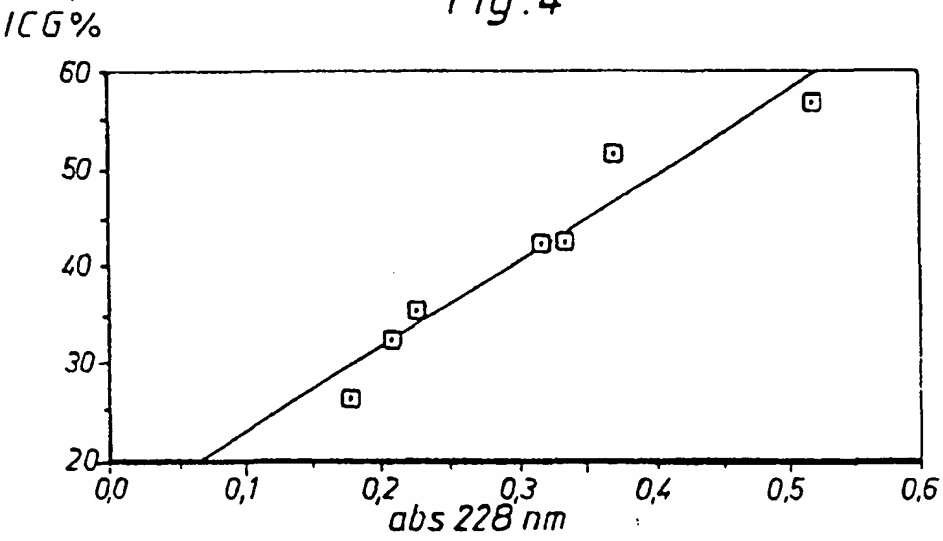


Fig.5

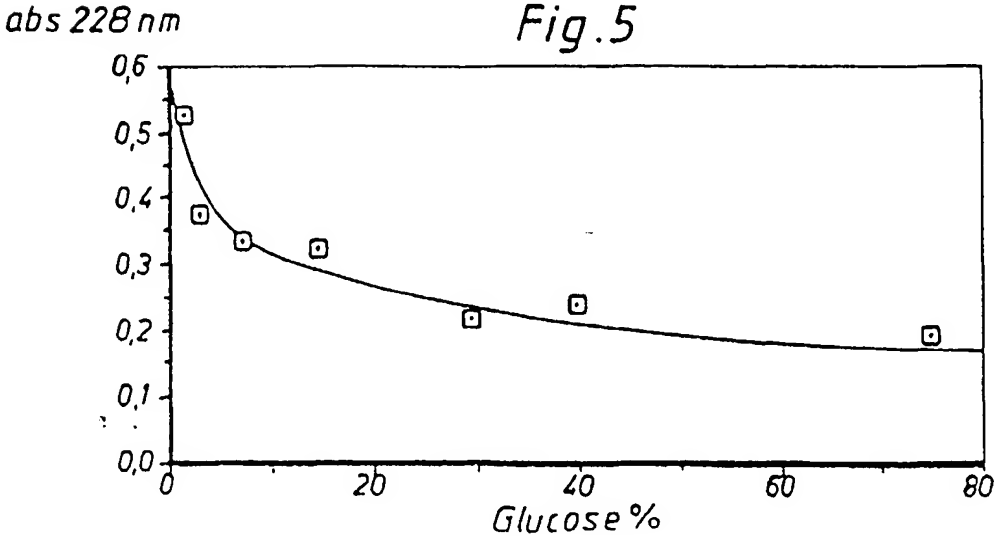


Fig. 6

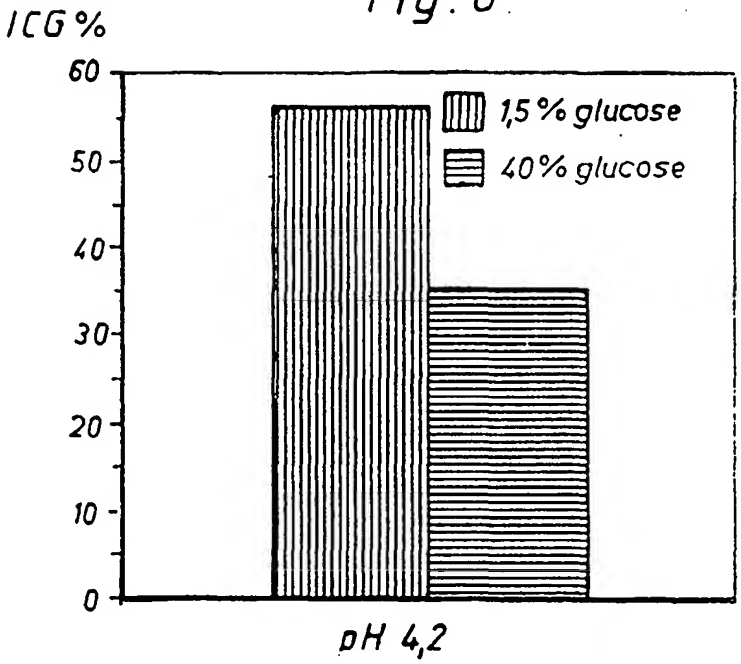
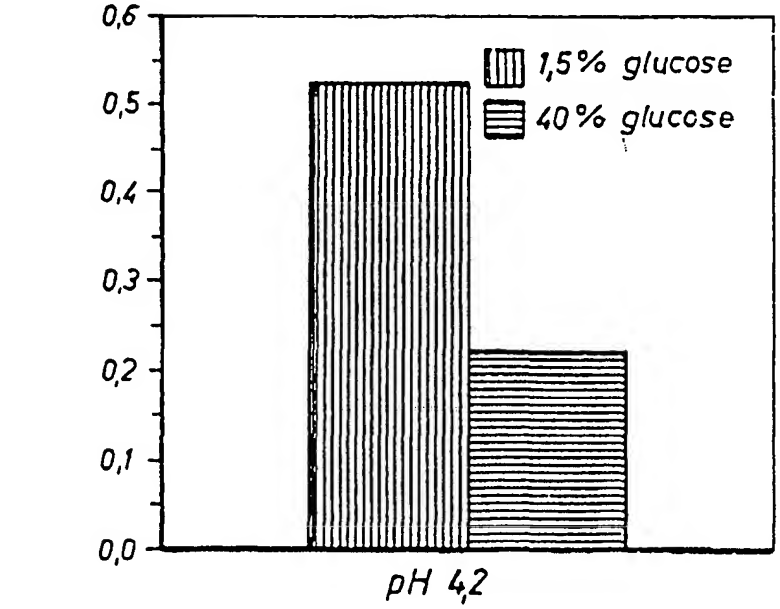

ICG %
60
50
40
30
20
10
0
1,5 % glucose
40 % glucose
pH 4,2

Fig. 7


abs 228 nm
0,6
0,5
0,4
0,3
0,2
0,1
0,0
1,5 % glucose
40 % glucose
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